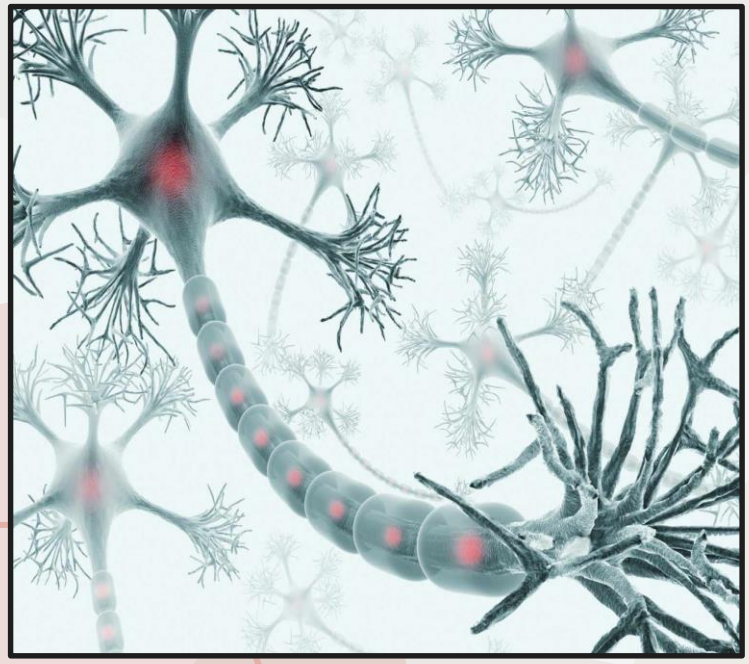

DIABETIC NEUROPATHY

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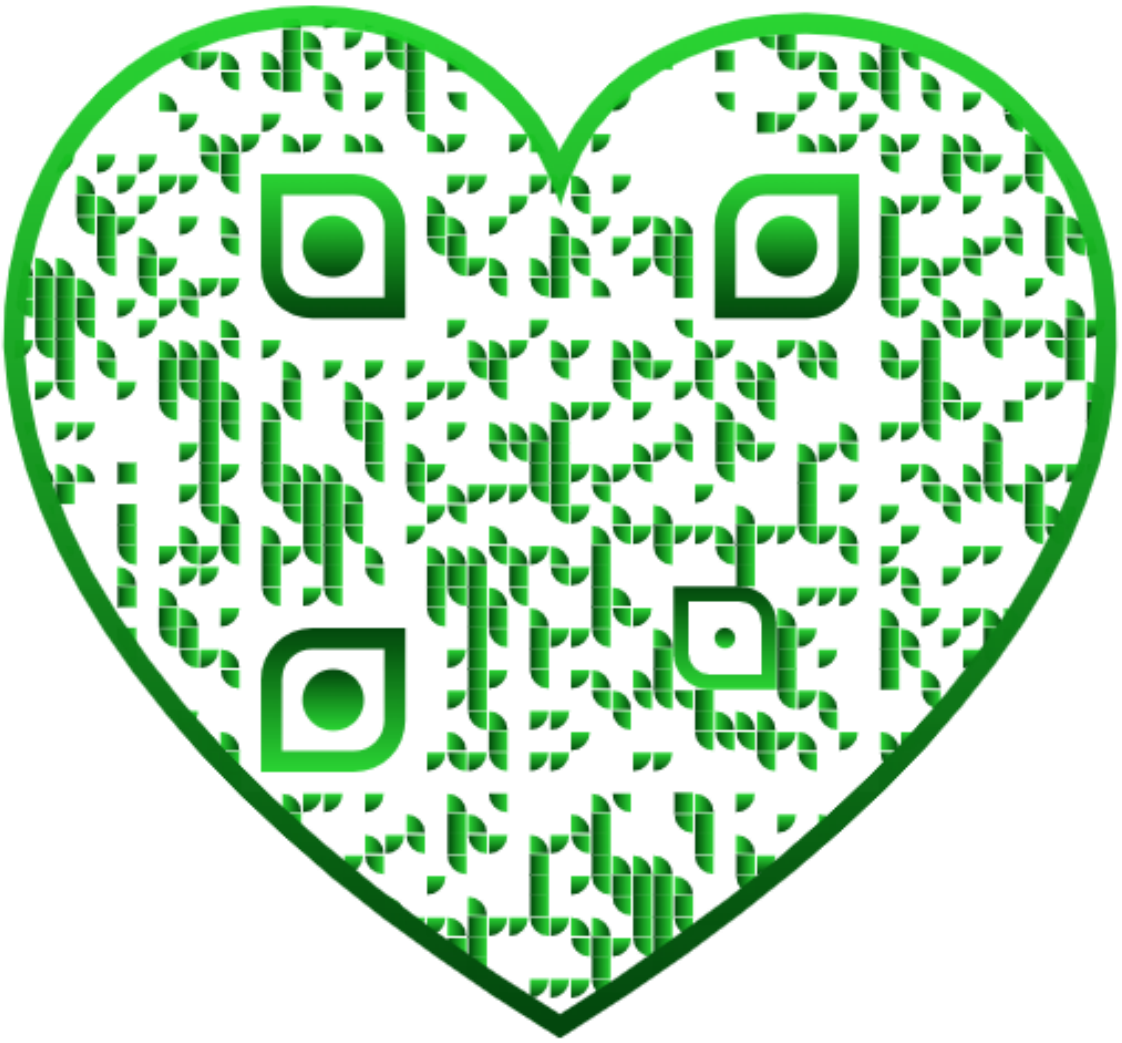


DEFINITION

An internationally agreed simple definition of Diabetic neuropathy for clinical practice is.

“the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes”

PATHOPHYSIOLOGY OF DPN

● Early injury and loss of small fibers, susceptible to energy flux, occur in people with diabetes, resulting in symptomatic pain and burning in their feet.

● As the disease progresses, larger nerve fibers also become injured by the lack of energy sources, and individuals experience numbness and loss of position sense in their feet.

● These signs and symptoms progress from the feet upward into the leg and reflect a distal-to proximal fiber loss that is the hallmark of diabetic neuropathy.

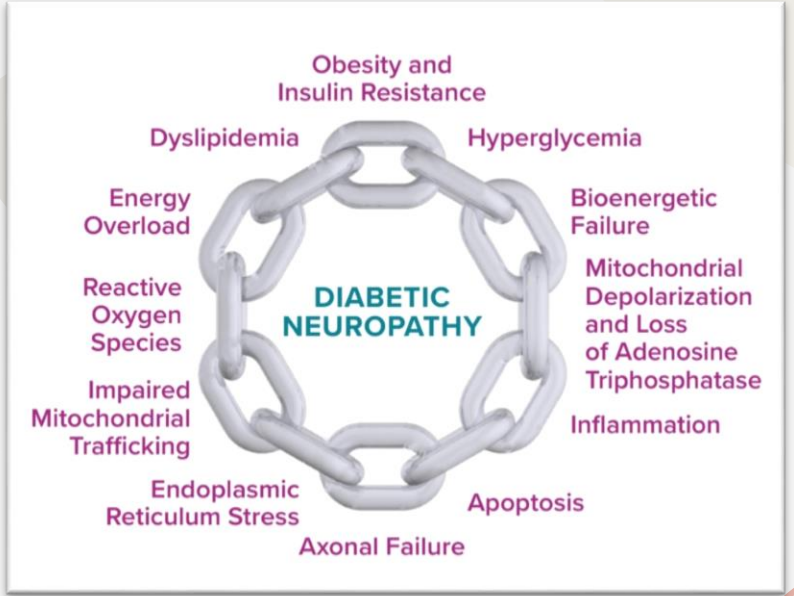


FIGURE 1 Chain of events underlying the pathophysiology of diabetic neuropathy.

SCREENING AND DIAGNOSING DPN

1 Take a Targeted History

Are risk factors present?
- Long diabetes duration
- Older age
- Metabolic syndrome
- Obesity
- Hyperlipidemia
- Tall stature
- Social determinants of health
- Frequent falls

yes

2 Assess for DPN Symptoms

Is neuropathic pain present?
- Burning
- Lancinating
- Shooting (electric shock-like)
- Worse at night
- Hyperalgesia

yes

Are symptoms of large-fiber DPN present?
- Numbness
- Poor balance
- Weakness

yes

3 Test for Clinical Signs of DPN

Are signs of small-fiber DPN present?
- Reduced/absent pinprick sensation
- Reduced/absent cold temperature sensation

Are signs of large-fiber DPN present?
- Reduced/absent vibration sensation
- Reduced/absent light touch sensation
- Reduced ankle reflexes

yes

Are symptoms and signs distributed in a symmetrical, length-dependent “stocking and glove” pattern?

No

Refer to neurologist

yes

DPN is present

4 Develop a Differential Diagnosis

Assess for factors

yes

DPN is likely

No

Treat underlying condition; refer for specialty care as needed

5 Perform Confirmatory Testing as Needed

Differential Diagnosis For Diabetic Peripheral Neuropathy.

Metabolic Disease
- Thyroid
- Renal

Systemic Disease
- Vasculitis
- Paraproteinemia
- Amyloidosis

Infectious Disease
- HIV
- Hepatitis B
- Lyme disease

Inflammatory Disease
- Chronic inflammatory demyelinating polyradiculoneuropathy

Nutrition
- Vitamin B12 deficiency
- Pyridoxine
- Thiamine
- Tocopherol

Industrial Agents
- Acrylamide
- Organophosphorous agents

Drugs
- Alcohol
- Amiodarone
- Chemotherapy

Heavy Metals
- Arsenic
- Mercury

Heredity/Genetics

SCREENING AND DIAGNOSING DPN

● DPN assessment should be performed annually starting at diagnosis for type 2 diabetes and 5 years after the diagnosis for type 1 diabetes. People with prediabetes and young people with symptoms or signs of DPN should also be screened.

● Assessment should include a detailed history and at least two sensation and reflex tests. Electrophysiological testing is rarely needed for people with typical signs and symptoms.

● A complex differential is recommended, and ambiguous or atypical cases should be referred to a neurologist and/or have additional testing.

TREATING PAINFUL DPN

● 30% of all individuals with DPN will experience painful symptoms that will require pharmacological and other treatments.

● More common in older patients.

● Younger individuals with poorly controlled type 1 diabetes, pain may be present with no or very few other clinical signs whereas older individuals are also likely to have large-fiber dysfunction, resulting in unsteadiness and gait disturbances, which can adversely affect activities of daily living.

Pain Assessment

●Visual analog scale (VAS) or a series of simple, orienting questions.

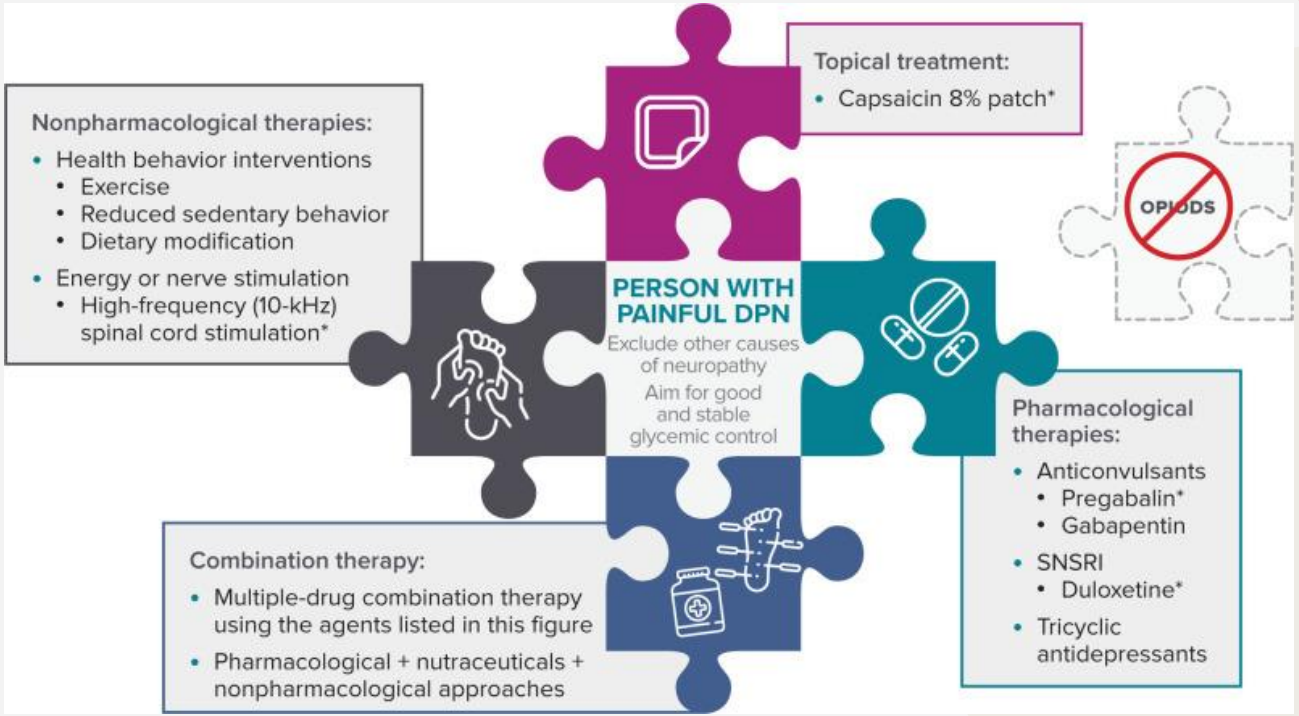
Acute Painful Diabetic Neuropathy

- It’s rare but well-recognized and distinct variety of the sensory neuropathies.
- Characterized by very severe neuropathic symptoms.
- Typically occur after a sudden change in glycemic control and has been described as occurring after normalization of blood glucose levels after simultaneous pancreas and kidney transplantation.
- It can also follow an episode of ketoacidosis, (mainly young female patients).
- The prognosis is mainly good, typically with resolution of symptoms within 12 months.

Chronic Painful Diabetic Neuropathy

- This chronic painful neuropathy is common among people of all ages with either type 1 or type 2 diabetes.

Therapeutic Approaches



Recommended therapeutic approaches to painful diabetic peripheral neuropathy.

FDA-Approved Pharmacological Treatments

● There are three FDA-approved therapies for painful DPN: pregabalin, duloxetine, and tapentadol.

► Pregabalin.

● The efficacy of which has been confirmed in a large number of studies, It has been extensively studied in painful DPN and evidence suggests a dose-dependent response, with weaker effect at lower doses.

● It can be given twice, or, on occasion, three times daily, and most patients require 300–600 mg/day for symptomatic relief.

● Great caution must be taken in individuals with renal impairment, especially those with an estimated glomerular filtration rate (eGFR) <45 mL/min/1.73 m2.

● Adverse effects, which commonly include somnolence, dizziness, and peripheral edema, are more likely with higher dosages and also in the elderly.

Cont. Treatment:

● It is common to start with 75 mg twice daily and gradually increase the dose every 3–7 days to a maximum of 600 mg/day.

● Greater caution is required in elderly patients, who are more likely to have renal dysfunction and in whom side effects are
more common; in these individuals, starting at 25 mg daily may be required.

● Because pregabalin additionally has anxiolytic activity, It may be particularly helpful in individuals with marked anxiety, which is not uncommon among people experiencing neuropathic pain.

► Duloxetine.

● Duloxetine is a selective norepinephrine and serotonin reuptake inhibitor and can be given once daily at a dose of either 60 or 120 mg.

● Its efficacy has been proven in a number of randomized controlled trials (RCTs), and it has been shown in head-to-head trials to have similar efficacy to other agents, including pregabalin and gabapentin .

Cont. Treatment:

● Its adverse effects are well recognized and include nausea, Somnolence, and dizziness, among others Because duloxetine and pregabalin have different modes of action, the combination of these agents has been used with good effect in clinical practice.

● However, The largest comparative trial did not show a significant difference between high-dose monotherapy With either agent and a standard-dose combination of both. However, there was a trend consistently favoring combination therapy over monotherapy. Because duloxetine is also an antidepressant, it may be Particularly helpful in people with painful DPN who also have depressive symptomatology.

► Other Pharmacological Therapies:

► Opioids.

Although several opioids have been shown to have some efficacy in the management of neuropathic pain in general, their associated high risks of addiction, abuse, Sedation, and other complications such as somnolence, Headache, and impaired gastrointestinal motility even in the short term are major barriers to their use.

Cont. Treatment:

►Amitriptyline.

● Amitriptyline and other tricyclic antidepressant agents have been used for many years in the management of neuropathic pain. However, adverse effects are common, especially in the elderly, and include anticholinergic effects such as dry mouth, urinary retention, and drowsiness. There are also warnings to use these agents with caution in the presence of ischemic heart disease or glaucoma.

● It can be given once daily, usually in the early evening, and the usual starting dose is 25 mg Increasing as necessary to a maximum of 150 mg. However, much lower doses must be used in older patients, and because of potential cardiovascular adverse effects, great caution should be taken in those with known ischemic heart disease.

►Gabapentin.

● Was first used as an anti-epileptic drug but has been shown to have efficacy in the management of painful DPN. However, it has a shorter half-life and therefore must be dosed three times daily. Lower doses are recommended for individuals with a reduced eGFR (45).

Cont. Treatment:

► **Topical Therapies:**

► **Capsaicin.**

● Recently, an 8% long-acting capsaicin patch has been developed and is now approved by the FDA for painful DPN.
● Fewer central adverse effects than the oral medications.
● May cause significant pain at the application site, it should be avoided in patients with active skin lesions.

Physical Therapies

● Spinal cord stimulation (SCS) in the management of severe painful DPN.

Cont. Treatment:

► **Combination Treatment.**

Pharmacological therapies:

- Anticonvulsants
  - Pregabalin
  - Gabapentin
- SNSRI
  - Duloxetine
- Tricyclic antidepressants

►ROLE OF NUTRACEUTICALS IN DPN AND PAIN MANAGEMENT

●It has been proposed that, unlike dietary supplements, nutraceuticals should not only supplement the diet, but also aid in the prevention and/or treatment of disease and/or disorder.

ROLE OF NUTRACEUTICALS IN DPN AND PAIN MANAGEMENT

● It has been proposed that, unlike dietary supplements, nutraceuticals should not only supplement the diet, but also aid in the prevention and/or treatment of disease and/or disorder.

► Effective pharmacological therapies for painful DPN include anti-epileptic agents (pregabalin and gapapentin) and anti-depressants (duloxetine and tricyclics), although often effective pain reduction requires higher doses that may be less tolerated or have a higher incidence of adverse effects.

► For those with severe painful symptoms not responding to a single agent, combination therapy with two to three agents may be effective at much lower doses, as well as combinations of pharmacological and nonpharmacological approaches. Such patients might also benefit from referral to a pain clinic if several attempts to control pain have failed.

► Given the high risk for complications and the modest evidence for benefit, the use of opioids is not recommended.

► Painful DPN is not uncommon in older people with diabetes, in whom caution must be taken with any prescribed medications. Starting at the lowest doses with slow up-titration is recommended in such cases.

Therapeutic Role of Nutraceuticals

► The rationale for using nutraceuticals in DPN is primarily to favorably influence the underlying neuropathic process and its clinical consequences rather than only relieving symptomatic pain, which is usually the goal of analgesic therapy. Which include:

- α-Lipoic Acid.
- Benfotiamine.
- Vitamin E.
- Vitamin B12.
- Acetyl-L- carnitine.
- Vitamin D.
- Polyunsaturated Fatty Acids.
- Magnesium.

Nutraceutical	Study	T1D, *n*/ T2D, *n*	Dose*	Duration	Effects	Adverse Events
α-Lipoic acid (ALA)	ALADIN (108)†	0/328	100/600/1,200/ placebo	3 weeks IV	Symptoms + Signs + QoL +	None
	ALADIN II (108)†	65‡	600/1,200/ placebo	2 years PO	NCS +	None
	ALADIN III (108)†	0/508	600 IV/1,800 PO/ placebo	3 weeks IV/ 6 months PO	Symptoms (+)/– Signs +/(+)	None
	ORPIL (108)†	0/24	1,800/placebo	3 weeks PO	Symptoms + QoL (+) Signs +	None
	SYDNEY (108)†	30/90	600/placebo	3 weeks IV	Symptoms + NSC + Signs +	None
	SYDNEY 2 (108)†	30/151	600/1,200/1,800/ placebo	5 weeks PO	Symptoms + NSC + Signs +	Dose-dependent GI symptoms
	NATHAN 1 (108)†	110/344	600/placebo	4 years PO	Signs + NCS –	SAEs slightly increased§
	El-Nahas et al. (109)	0/200	1,200/placebo	6 months PO	Symptoms + VPT +	Mild nausea
Benfotiamine	BENDIP (102)†	16/117	300/600/placebo	6 weeks	Symptoms + (PP) Signs –	None
	BEDIP (102)†	8/32	400/placebo	3 weeks	Symptoms/signs + Pain +	None
Vitamin B12	Didangelos et al. (112)	0/90	1/placebo	1 year	Symptoms + Signs – Pain + VPT + NCS +	None
Vitamin D	Karonova et al. (114)	0/67	40,000 IU/ 5,000 IU per week	24 weeks	Pain + Symptoms + Signs +	None
Vitamin E	VENUS (116)	300‡	400/placebo	1 year	Symptoms – Lancinating pain (+)	None
Acetyl-L-carnitine	Sima et al. (118)	1,257‡	3,000/placebo	1 year	Pain + VPT + NCS –	None
γ-Linolenic acid (GLA)	Keen et al. (119)	57/51	480/placebo	1 year	NCS + Signs +	None
	Won et al. (120)	0/100	320 GLA/ 600 ALA	12 weeks	Symptoms, pain noninferior‖	None
Magnesium	de Leeuw et al. (122)	110/0	300/ no supplement	5 years	DPN stage +¶ NCS +	GI symptoms

NONPHARMACOLOGICAL APPROACHES TO DPN AND PAIN MANAGEMENT

► Fall into three categories:

1. Health behavior interventions (HBIs), including exercise, dietary counseling, and their combination.

2. Passive modalities, including neuro-biofeedback ,foot bath techniques , and static magnetic fields.

3. Nonpharmacological energy or nerve stimulation treatments.
   - Electromagnetic Stimulation Modalities
   - Spinal Cord Stimulation
   - Transcranial Magnetic Stimulation
   - Transcutaneous Electrical Nerve Stimulation
   - Systematic Surgical Decompression
   - Acupuncture
   - Photon Stimulation

Cont. NONPHARMACOLOGICAL APPROACHES.

- Regular aerobic, strengthening, and balance exercise, alone or in combination; reduction of sedentary behavior; and dietary modification aimed at reducing calorie intake and increasing plant-based foods and polyunsaturated fats have all demonstrated positive outcomes for individuals with DPN.

- Exercise participation, guided by exercise prescription and supervision by an exercise specialist, is safe and can improve exercise behaviors and reduce the risk for exercise associated injury.

- SCS and high-frequency SCS provide long-lasting reduction in neuropathic pain in people with DPN pain refractory to medical therapy but must be balanced against serious potential complications in this population.

Practical Cases

Case 1

A 68-year-old man with a 7-year history of diabetes mellitus. His other medical problem is BPH. **Fasting blood glucose was 150 mg/dl, and his HbA1c was 7.8%.** He is on sitagliptine /metformin 50/850 mg O.D.

Approximately 3 months ago, he noticed some burning and tingling in his feet. He admitted that he had not felt as well as usual and that his walking was becoming more of a chore. His physical examination was normal except for some hyperesthesia of both feet as well as decreased vibratory sensation. His thyroid, reflexes, and pulses were normal.

How do you manage such a case?

A) Change diabetes drugs in order to make good control.
B) Add vitamin E, which acts as anti oxidative drugs to relive the pain.
C) Start vitamin B12 with pregabalin.
D) Start vitamin B12 with amitriptyline.
E) You will do nothing, only observation.

Case 2

A 45-year-old female with a 20-year history of diabetes mellitus type I. **Fasting blood glucose was 123 mg/dl, and her HbA1c was 7.2%. On mixtard insulin.** Presented to the clinic complaining of burning and tingling in her hands and feet that started approximately 4 months ago but became worse a week ago. Was seen by endocrinologist. And Started **pregabalin 75 mg once daily, Vitamin B12 and Benfotiamine**. Her physical examination was unremarkable except for some hyperesthesia of both hands and feet as well as decreased vibratory sensation.

How do you manage such a case?

A) Change pregabalin to duloxetine.
B) Add vitamin D supplement even if is within normal level.
C) Stop vitamin B12 and continue on pregabalin.
D) Continue with same treatment and increase the pregabalin dose to 150 mg O.D.
E) Stop vitamin B12 and add duloxetine beside pregabalin, for more beneficial effect.

Case 3

A 32-year-old male patient with BMI of 32 kg/m^2 who's recently diagnosed with – Diabetes mellitus (MOD). **Fasting blood glucose was 115 mg/dl, and his HbA1c was 10%.** Started on Dapagliflozin with metformin 10/1000 mg O.D since 2 weeks ago.

About one year ago, he noticed some burning sensation, restless and tingling in his feet and was seen by neurologist and diagnosed as a case of restless leg syndrome, **was prescribed Gapapentin 300 mg once daily,** and there was mild relief. Patient now is worry about the diabetes mellitus complication 'Neuropathic complications" and request some medical advices and proper treatment.

How do you manage such a case?

A) Change Gapapentin to pregabalin.
B) Check vitamin D3 level and treat it accordingly.
C) Stop dapagliflozine /metformin and start sulfonylureas such as gliclazide.
D) Continue with same treatment and increase the gabapentin dose to 300 mg T.D.S.
E) Stop gabapentin and start Benfotiamine 300 mg O.D for 6 months.

Case 4

A 55-year-old man with 15-year history of diabetes mellitus type II. On oral medications metformin 500 mg O.D and glimepiride 3 mg O.D. Complicated with retinopathy, neuropathy and nephropathy the eGFR 40 ml/min/1.73m^2. His other medical problem is BPH and Glaucoma.

Approximately 2 months ago, he noticed a burning and tingling in his hands and feet, felt that this sense of balance was diminished and was diagnosed as a case of diabetic polyneuropathy. The medical decision that should be made is:

A)Start pregabalin 75 mg and increase the dose gradually every 3 to 7 days based on pain response.
B) Start Benfotiamine.
C) Start combination therapy pregabalin 75 mg with duloxetine 30 mg.
D) Start Gapapentin 300 mg twice a day.
E) Start with caution duloxetine 60 mg once O.D.

Thank you for your attendance